

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Err ors
1	BRS	L1	218	botulinum adj (toxin or neurotoxin)	USPAT; EPO; JPO; Derwent	2000/12/08 17:51			0
2	BRS	L2	9	clostridial adj neurotoxin	USPAT; EPO; JPO; Derwent	2000/12/08 17:52			0
3	BRS	L3	5217	neuropeptide or neurotransmitter or (neurotransmission adj compound)	USPAT; EPO; JPO; Derwent	2000/12/08 17:53			0
4	BRS	L4	3130	tachykinin or (substance adj P)	USPAT; EPO; JPO; Derwent	2000/12/08 17:55			0
5	BRS	L5	415	physalaemin or kassinin or uperolein or eledoisin or (substance adj K)	USPAT; EPO; JPO; Derwent	2000/12/08 17:59			0
6	BRS	L7	12	1 same 3	USPAT	2000/12/08 18:01			0
7	BRS	L8	1	1 same 4	USPAT	2000/12/08 18:02			0
8	BRS	L9	0	1 same 5	USPAT	2000/12/08 18:02			0
9	BRS	L10	0	2 same 5	USPAT	2000/12/08 18:02			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
10	BRS	L11	2	2 same 3	USPAT	2000/12/08 18:02			0
11	BRS	L12	0	2 same 4	USPAT	2000/12/08 18:02			0

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NEWS 4 Oct 27 SET ABBREVIATIONS and SET PLURALS extended in
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NEWS 5 Oct 27 Patent Assignee Code Dictionary now available
in Derwent Patent Files
NEWS 6 Oct 27 Plasdoc Key Serials Dictionary and Echoing added to
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=> s botulinum (w) (toxin or neurotoxin)

L1 15337 BOTULINUM (W) (TOXIN OR NEUROTOXIN)

=> s clostridial neurotoxin

L2 738 CLOSTRIDIAL NEUROTOXIN

=> s neuropeptide or neurotransmitter or neurotransmission compound

L3 276657 NEUROPEPTIDE OR NEUROTRANSMITTER OR NEUROTRANSMISSION COMPOUND

=> s tachykinin or substance (w) P

L4 94483 TACHYKININ OR SUBSTANCE (W) P

=> s physalaemin or kassinin or uperolein or eledoisin or substance (w) K

L5 5148 PHYSALAEAMIN OR KASSININ OR UPEROLEIN OR ELEDOISIN OR SUBSTANCE
(W) K

=> s l1 (p) l3

L6 688 L1 (P) L3

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L7 231 DUPLICATE REMOVE L6 (457 DUPLICATES REMOVED)

=> s l7 (p) (conjugate or covalent)

L8 4 L7 (P) (CONJUGATE OR COVALENT)

=> d l8 1-4 ibib abs

L8 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 2000:282545 CAPLUS

DOCUMENT NUMBER: 133:54741

TITLE: Inhibition of vesicular secretion in both neuro¹
and Page 2

substanceP-pain

AUTHOR(S): nonneuronal cells by a retargeted endopeptidase derivative of Clostridium botulinum neurotoxin type A
Chaddock, John A.; Purkiss, John R.; Friis, Lorna M.; Broadbridge, Janice D.; Duggan, Michael J.; Fooks, Sarah J.; Shone, Clifford C.; Quinn, Conrad P.; Foster, Keith A.
CORPORATE SOURCE: Centre for Applied Microbiology and Research, Salisbury, SP4 0JG, UK
SOURCE: Infect. Immun. (2000), 68(5), 2587-2593
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Clostridial neurotoxins potentially and specifically inhibit **neurotransmitter** release in defined cell types by a mechanism that involves cleavage of specific components of the vesicle docking/fusion complex, the SNARE complex. A deriv. of the type A neurotoxin from C. botulinum (termed LHN/A) that retains catalytic activity can be prep'd. by proteolysis. The LHN/A, however, lacks the putative native binding domain

(HC) of the neurotoxin and is thus unable to bind to neurons and effect inhibition of **neurotransmitter** release. Here, the authors report the chem. conjugation of LHN/A to an alternative cell-binding ligand, wheat germ agglutinin (WGA). When applied to a variety of cell lines, including those that are ordinarily resistant to the effects of neurotoxin, WGA-LHN/A **conjugate** potentially inhibits secretory responses in those cells. Inhibition of release is demonstrated to be ligand-mediated and dose-dependent and to occur via a mechanism involving endopeptidase-dependent cleavage of the natural **botulinum neurotoxin** type A substrate. These data confirm that the function of the HC domain of C. **botulinum neurotoxin** type A is limited to binding to cell surface moieties. The data also demonstrate that the endopeptidase and translocation functions of the neurotoxin are effective in a range of cell types, including those of nonneuronal origin.

These observations lead to the conclusion that a clostridial endopeptidase **conjugate** that can be used to investigate SNARE-mediated processes in a variety of cells has been successfully generated.

REFERENCE COUNT: 30

REFERENCE(S): (1) Black, J; Neuroscience 1987, V23, P767 CAPLUS
(2) Blasi, J; Nature 1993, V365, P160 CAPLUS
(3) Boyd, R; J Biol Chem 1995, V270, P18216 CAPLUS
(4) Fitzgerald, D; Targeted Diagn Ther 1992, V7, P447 CAPLUS
(6) Gabor, F; J Controlled Release 1998, V55, P131 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 2000:144760 CAPLUS

DOCUMENT NUMBER: 132:175838

TITLE: Compounds inhibiting exocytosis in mucus-secreting cells or neurotransmitter release from neurons that control or direct mucus secretion for treatment of mucus hypersecretion

INVENTOR(S): Quinn, Conrad Padraig; Foster, Keith Alan; Chaddock

substanceP-pain

John Andrew
 PATENT ASSIGNEE(S): Microbiological Research Authority, UK
 SOURCE: PCT Int. Appl., 30 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000010598	A2	20000302	WO 1999-GB2806	19990825
WO 2000010598	A3	20000615		
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9955250	A1	20000314	AU 1999-55250	19990825
PRIORITY APPLN. INFO.:			GB 1998-18548	19980825
			WO 1999-GB2806	19990825

AB A method of treating mucus hypersecretion, the causative factor in chronic obstructive pulmonary disease (COPD), asthma, and other clin. conditions involving COPD, comprises administering a compd. that inhibits exocytosis in mucus secreting cells or neurons that control or direct mucus secretion. Also described is a compd., for use in the treatment of hypersecretion of mucus, which inhibits mucus secretion by inhibiting mucus secretion by mucus secreting cells, and/or inhibiting neurotransmitter release from neuronal cells controlling or directing mucus secretion.

L8 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2000 ACS
 ACCESSION NUMBER: 1996:743984 CAPLUS
 DOCUMENT NUMBER: 126:1210
 TITLE: Botulin derivative or other agent able to inhibit neuromodulator secretion by sensory afferent synapses and agent use as pain inhibitor
 INVENTOR(S): Foster, Keith Alan; Duggan, Michael John; Shone, Clifford Charles
 PATENT ASSIGNEE(S): The Speywood Laboratory Limited, UK; Microbiological Research Authority
 SOURCE: PCT Int. Appl., 43 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9633273	A1	19961024	WO 1996-GB916	19960416
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
CA 2218857	AA	19961024	CA 1996-2218857	19960416

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AU 9653398 A1 19961107 AU 1996-53398 19960416
 AU 705924 B2 19990603
 EP 826051 A1 19980304 EP 1996-910091 19960416
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,
 SI, LT, LV, FI
 CN 1187217 A 19980708 CN 1996-194505 19960416
 JP 11504006 T2 19990406 JP 1996-531546 19960416
 BR 9609870 A 19990406 BR 1996-9870 19960416
 ZA 9603129 A 19961022 ZA 1996-3129 19960419
 NO 9704845 A 19971218 NO 1997-4845 19971020
 US 5989545 A 19991123 US 1998-945037 19980112
 GB 1995-8204 19950421
 WO 1996-GB916 19960416

PRIORITY APPLN. INFO.:

AB The invention relates to an agent specific for peripheral sensory afferents. The agent may inhibit the transmission of signals between a primary sensory afferent and a projection neuron by controlling the release of at least one **neurotransmitter** or neuromodulator from the primary sensory afferent. The agent may be used in or as a pharmaceutical for the treatment of pain, particularly chronic pain. An example is Clostridium **botulinum neurotoxin** (BoNT) **conjugates** with nerve growth factor (NGF). The BoNT/NGF **conjugate** specifically interacts with sensory afferents and the proteinase activity of the BoNT/NGF **conjugate** cleaves proteins involved in neuromodulator secretion.

L8 ANSWER 4 OF 4 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 2000346869 EMBASE
 TITLE: A **conjugate** composed of nerve growth factor coupled to a non-toxic derivative of Clostridium **botulinum neurotoxin** type A can inhibit **neurotransmitter** release in vitro.
 AUTHOR: Chaddock J.A.; Purkiss J.R.; Duggan M.J.; Quinn C.P.; Shone C.C.; Foster K.A.
 CORPORATE SOURCE: J.R. Purkiss, Centre for Applied Microbiology/Res., Porton Down, Salisbury, Wiltshire SP4 0JG, United Kingdom
 SOURCE: Growth Factors, (2000) 18/2 (147-155).
 Refs: 24
 ISSN: 0897-7194 CODEN: GRFAEC
 COUNTRY: United Kingdom
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 030 Pharmacology
 037 Drug Literature Index
 039 Pharmacy
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 AB Nerve growth factor (NGF) receptor binding, internalisation and transportation of NGF has been identified as a potential route of delivery for other molecules. A derivative of Clostridium **botulinum neurotoxin** type A (LH(N)) that retains catalytic activity but has significantly reduced cell-binding capability has been prepared and chemically coupled to NGF. Intact clostridial neurotoxins potently inhibit **neurotransmitter** release at the neuromuscular junction by proteolysis of specific components of the vesicle docking/fusion complex. Here we report that the NGF-LH(N)/A **conjugate**, when applied to

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PC12 cells, significantly inhibited **neurotransmitter** release and cleaved the type A toxin substrate. This work represents the successful use of NGF as a targeting moiety for the delivery of a neurotoxin fragment.

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FILE 'CAPLUS, MEDLINE, EMBASE, BIOSIS, SCISEARCH' ENTERED AT 18:11:36 ON 08 DEC 2000

L1 15337 S BOTULINUM (W) (TOXIN OR NEUROTOXIN)
L2 738 S CLOSTRIDIAL NEUROTOXIN
L3 276657 S NEUROPEPTIDE OR NEUROTRANSMITTER OR NEUROTRANSMISSION
COMPOUN
L4 94483 S TACHYKININ OR SUBSTANCE (W) P
L5 5148 S PHYSALAEMIN OR KASSININ OR UPEROLEIN OR ELEDOSIN OR
SUBSTANC
L6 688 S L1 (P) L3
L7 231 DUPLICATE REMOVE L6 (457 DUPLICATES REMOVED)
L8 4 S L7 (P) (CONJUGATE OR COVALENT)

=> s 17 (p) (link or linkage)

L9 4 L7 (P) (LINK OR LINKAGE)

=> d 19 1-4 ibib abs

L9 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1997:81926 CAPLUS

DOCUMENT NUMBER: 126:166737

TITLE: Cleavage of syntaxin prevents G-protein regulation of presynaptic calcium channels

AUTHOR(S): Stanley, E. F.; Mirotznik, R. R.

CORPORATE SOURCE: Natl. Inst. Neurological Diseases and Stroke, Natl. Inst. Health, Bethesda, MD, 20892, USA

SOURCE: Nature (London) (1997), 385(6614), 340-343

CODEN: NATUAS; ISSN: 0028-0836

PUBLISHER: Macmillan Magazines

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Neurotransmitter** release into the synapse is stimulated by calcium influx through ion channels that are closely assocd. with the transmitter release sites. This **link** may involve the membrane protein syntaxin, which is known to be assocd. with the release sites and to bind to the calcium channels. There is evidence that presynaptic calcium channels are downregulated by second messenger pathways involving G proteins. Here the authors use the path-clamp technique to test

whether

calcium current is regulated by G proteins in a vertebrate presynaptic nerve terminal, and whether this regulation is affected by the **linkage** to syntaxin. The calcium current in the nerve terminal showed typical G-protein-mediated changes in amplitude and activation kinetics which were reversed by a preceding depolarization. These

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of the G protein were virtually eliminated if syntaxin was first cleaved with **botulinum toxin C1**. The findings indicate that this sensitivity of the current to modulation by G proteins requires the assocn. of the presynaptic calcium channel with elements of the transmitter release site, which may ensure that channels tethered at release sites are preferentially regulated by the G-protein second messenger pathway.

L9 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1994:263475 CAPLUS

DOCUMENT NUMBER: 120:263475

TITLE: Exogenous zinc ion is required for inhibitory activity

of botulinum neurotoxin C1 against norepinephrine release and its endopeptidase activity toward substance P

AUTHOR(S): Yokosawa, Noriko; Suga, Kei; Kimura, Koichi; Tsuzuki, Kayo; Fujii, Nobuhiro; Oguma, Keiji; Yokosawa, Hideyoshi

CORPORATE SOURCE: Sch. Med., Sapporo Med. Univ., Sapporo, 060, Japan
SOURCE: Biochem. Mol. Biol. Int. (1994), 32(3), 455-63
CODEN: BMBIES

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Botulinum neurotoxin C1** inhibited Ca^{2+} -evoked norepinephrine secretion from digitonin-permeabilized PC12 cells. The inhibition by the neurotoxin was dependent on the presence of Zn^{2+} added exogenously. This zinc-dependent inhibition was neutralized by monoclonal

antibodies that recognize the sites close to the putative zinc-binding motif in the light chain. The neurotoxin was found to have an endopeptidase activity toward small peptide, substance P. The presence of

exogenous Zn^{2+} was also indispensable to the full expression of this endopeptidase activity. Thus, both the inhibition of **neurotransmitter** release by the C1 neurotoxin and its endopeptidase activity are dependent on exogenous Zn^{2+} , which suggests a strong link between the two activities.

L9 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1994:47773 CAPLUS

DOCUMENT NUMBER: 120:47773

TITLE: Botulinum neurotoxins serotypes A and E cleave SNAP-25

at distinct COOH-terminal peptide bonds

AUTHOR(S): Schiavo, Giampietro; Santucci, Annalisa; Dasgupta, Bibhuti R.; Mehta, Prashant P.; Jontes, Jaime; Benfenati, Fabio; Wilson, Michael C.; Montecucco, Cesare

CORPORATE SOURCE: Centro CNR Biomembrane e Dipartimento di Scienze Biomediche, Universita di Padova, Via Trieste, Padova,

75-35121, Italy

SOURCE: FEBS Lett. (1993), 335(1), 99-103

CODEN: FEBLAL; ISSN: 0014-5793

DOCUMENT TYPE: Journal

LANGUAGE: English

substanceP-pain

AB SNAP-25, a membrane-assocd. protein of the nerve terminal, is specifically cleaved by **botulinum neurotoxins** serotypes A and E, which cause human and animal botulism by blocking **neurotransmitter** release at the neuromuscular junction. Here the authors show that these two metallo-endorpeptidase toxins cleave SNAP-25 at two distinct carboxyl-terminal sites. Serotype A catalyzes the hydrolysis of the Gln197-Arg198 peptide bond, while serotype E cleaves the Arg180-Ile181 peptide **linkage**. These results indicate that the carboxyl-terminal region of SNAP-25 plays a crucial role in the multi-protein complex that mediates vesicle docking and fusion at the nerve terminal.

L9 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1993:619432 CAPLUS

DOCUMENT NUMBER: 119:219432

TITLE: Botulinum type A neurotoxin digested with pepsin yields 132, 97, 72, 45, 42, and 18 kD fragments

AUTHOR(S): Gimenez, Juan A.; DasGupta, Bibhuti R.

CORPORATE SOURCE: Dep. Food Microbiol. Toxicol., Univ. Wisconsin, Madison, WI, 53706, USA

SOURCE: J. Protein Chem. (1993), 12(3), 351-63

CODEN: JPCHD2; ISSN: 0277-8033

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Botulinum neurotoxin** (NT) serotype A is a dichain protein made of a light and a heavy chain linked by at least one interchain disulfide; based on SDS-polyacrylamide gel electrophoresis their mol. masses appear as 147, 52, and 93 kDa, resp. Digestion of the NT with pepsin under controlled pH (4.3 and 6.0), time (1 and 24 h), and temp. (25 and 30.degree.) produced 132, 97, 42, and 18 kDa fragments.

The

three larger fragments were isolated by ion-exchange chromatog. The 132 and 97 kDa fragments are composed of 52 kDa light chain and 72 and 45 kDa fragments of the heavy chain, resp. The sequences of amino terminal residues of these fragments were detd. to identify the pepsin cleavage sites in the NT, which based on nucleotide sequence has 1295 amino acid residues. The 42 kDa fragment, beginning with residue 866, is the C-terminal half of the heavy chain. The 18 kDa fragment, of which the first 72 residues were identified beginning with residue 1147, represents the C-terminal segment of the heavy chain. The 132 kDa fragment (residue 1 to .apprx.1146) is thus a truncated version of the NT without its 18

kDa

C-terminal segment. The 97 kDa fragment (residue 1 to .apprx.865) is

also

a truncated NT with its 42 kDa C-terminal segment excised. These peptic fragments contain one or two of the three functional domains of the NT (binds receptors, forms channels, and intracellularly inhibits exocytosis of the **neurotransmitter**) that can be used for structure-function studies of the NT. This report also demonstrates for the first time that of the six Cys residues 453, 790, 966, 1059, 1234, and 1279 located in

the

heavy chain the later four do not form interchain disulfide **links** with the light chain; however, Cys 1234 and 1279 contained within the 18 kD fragment form intrachain disulfide. The electrophoretic behaviors of type A NT and its fragments in native gels and their comparison with botulinum NT serotypes B and E as well as tetanus NT suggest that each NT

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forms dimers or other aggregates and the aggregation does not occur when the 42 kDa C-terminal half of the heavy chain is excised. Thus, the C-terminal half of the heavy chain appears important in the self-assocn. to form dimers.

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FILE 'CAPLUS, MEDLINE, EMBASE, BIOSIS, SCISEARCH' ENTERED AT 18:11:36 ON 08 DEC 2000

L1 15337 S BOTULINUM (W) (TOXIN OR NEUROTOXIN)
L2 738 S CLOSTRIDIAL NEUROTOXIN
L3 276657 S NEUROPEPTIDE OR NEUROTRANSMITTER OR NEUROTRANSMISSION
COMPOUN
L4 94483 S TACHYKININ OR SUBSTANCE (W) P
L5 5148 S PHYSALAEMIN OR KASSININ OR UPEROLEIN OR ELEDOSIN OR
SUBSTANC
L6 688 S L1 (P) L3
L7 231 DUPLICATE REMOVE L6 (457 DUPLICATES REMOVED)
L8 4 S L7 (P) (CONJUGATE OR COVALENT)
L9 4 S L7 (P) (LINK OR LINKAGE)

=> s l1 (p) l4

L10 44 L1 (P) L4

=> duplicate remove

ENTER L# LIST OR (END):l10

DUPLICATE PREFERENCE IS 'CAPLUS, MEDLINE, EMBASE, BIOSIS, SCISEARCH'
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PROCESSING COMPLETED FOR L10

L11 15 DUPLICATE REMOVE L10 (29 DUPLICATES REMOVED)

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L11 ANSWER 1 OF 15 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:323250 CAPLUS
DOCUMENT NUMBER: 132:303493
TITLE: Application of botulinum toxin to the management of
neurogenic inflammatory disorders
INVENTOR(S): First, Eric R.
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.

KIND DATE

APPLICATION NO. DATE

substanceP-pain

 US 6063768 A 20000516 US 1997-923884 19970904
 PRIORITY APPLN. INFO.: US 1996-20400 19960906

AB A method is provided for the use of at least one serotype or a combination of serotypes of botulinum neurotoxin either alone or in combination with other peptides or fusion proteins, that when administered in a safe and effective amt., antagonize and therefore decrease or block inflammation induced by the neurogenic mechanisms underlying or assocd. with inflammatory disorders, in particular, arthritis.

REFERENCE COUNT: 10
 REFERENCE(S): (1) Anon; WO 9517904 1995
 (2) Anon; WO 9528171 1995 CAPLUS
 (4) Binder; US 5670484 1997 CAPLUS
 (7) Leppla; US 5677274 1997 CAPLUS
 (8) Lianga; J Rheumatol 1986, V13(1), P230 MEDLINE
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 1
 ACCESSION NUMBER: 2000:221492 CAPLUS
 DOCUMENT NUMBER: 133:13529
 TITLE: Capsaicin-stimulated release of substance P from cultured dorsal root ganglion neurons: involvement of two distinct mechanisms
 AUTHOR(S): Purkiss, J.; Welch, M.; Doward, S.; Foster, K.
 CORPORATE SOURCE: CAMR (Centre for Applied Microbiology and Research), Porton Down, Salisbury, Wiltshire, UK
 SOURCE: Biochem. Pharmacol. (2000), 59(11), 1403-1406
 CODEN: BCPA6; ISSN: 0006-2952
 PUBLISHER: Elsevier Science Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Capsaicin, the pungent component of hot chili peppers, selectively activates a distinct population of primary sensory neurons responsive to noxious stimuli. Many of these fibers express neuropeptides including the **tachykinin, substance P**. Using cultured dorsal root ganglion neurons, the authors found that capsaicin (10 .mu.M) stimulated a 2-fold increase in the release of **substance P** in the absence of extracellular Ca²⁺. Elevated potassium (75 mM) was unable to induce the release under these conditions. The introduction of Ca²⁺ enhanced capsaicin-induced release and brought about a robust response to potassium. Preincubation of cells with **botulinum neurotoxin A** (100 nM) completely blocked the potassium-induced release but the capsaicin response, in the absence of Ca²⁺, was unaffected. However, toxin treatment dramatically reduced capsaicin-stimulated release in the presence of Ca²⁺. Thus, capsaicin induces the release of **substance P** from dorsal root ganglion neurons via 2 mechanisms, 1 requiring extracellular Ca²⁺ and the intact synaptosomal-assocd. protein 25 kDa (SNAP-25) and the other independent of extracellular Ca²⁺ and not involving SNAP-25.

REFERENCE COUNT: 16
 REFERENCE(S): (1) Bordier, C; J Biol Chem 1981, V256, P1604 CAPLUS
 (2) Caterina, M; Nature 1997, V389, P816 CAPLUS
 (3) Chard, P; Neuroscience 1995, V65, P1099 CAPLUS
 (4) Chen, F; Biochemistry 1997, V36, P5719 CAPLUS
 (5) Davletov, B; EMBO J 1998, V17, P3909 CAPLUS

substanceP-pain

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 15 SCISEARCH COPYRIGHT 2000 ISI (R)
ACCESSION NUMBER: 2000:530062 SCISEARCH
THE GENUINE ARTICLE: 309RU
TITLE: Enhanced **substance P** response of
botulinum toxin-injected opossum lower
esophageal sphincter.
AUTHOR: Gaumnitz E A (Reprint); Bass P; Osinski M A
CORPORATE SOURCE: UNIV WISCONSIN, SCH PHARM, MADISON, WI; UNIV WISCONSIN,
SCH MED, MADISON, WI; UNIV WISCONSIN, SCH PHARM, MADISON,
WI
COUNTRY OF AUTHOR: USA
SOURCE: GASTROENTEROLOGY, (APR 2000) Vol. 118, No. 4, Part 1,
Supp. [2], pp. 889-889.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST
CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L11 ANSWER 4 OF 15 SCISEARCH COPYRIGHT 2000 ISI (R)
ACCESSION NUMBER: 2000:268106 SCISEARCH
THE GENUINE ARTICLE: 299PQ
TITLE: Ultrastructural localization of the binding fragment of
tetanus toxin in putative gamma-aminobutyric acidergic
terminals in the intermediolateral cell column: A
potential basis for sympathetic dysfunction in
generalized
tetanus
AUTHOR: Ligorio M A; Akmentin W; Gallery F; Cabot J B (Reprint)
CORPORATE SOURCE: SUNY STONY BROOK, DEPT NEUROBIOL & BEHAV, STONY BROOK, NY
11794 (Reprint); SUNY STONY BROOK, DEPT NEUROBIOL &
BEHAV,
STONY BROOK, NY 11794
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF COMPARATIVE NEUROLOGY, (17 APR 2000) Vol. 419,
No. 4, pp. 471-484.
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605
THIRD AVE, NEW YORK, NY 10158-0012.
ISSN: 0021-9967.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 88

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Tetanus toxin (TeTx) causes sympathetic hyperactivity, a major cause
of
mortality in generalized tetanus, apparently by obstructing the
inhibition
of sympathetic preganglionic neurons (SPNs). Neuroanatomic tracing and
immunohistochemistry were used to investigate whether axon terminals in
the intermediolateral cell column (IML) that synapse on SPNs and use the
inhibitory neurotransmitter gamma-aminobutyric acid (GABA) may be
infected

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transsynaptically with TeTx. The binding fragment of TeTx (TTC; an atoxic surrogate of TeTx) and the cholera toxin B subunit (CTB; a retrograde tracer) were injected into the rat superior cervical ganglion and, over 16-48 hours, were transported to the ipsilateral IML in the caudal half of the last cervical and first three thoracic spinal cord segments. With light microscopy, diffuse CTB immunolabeling extended throughout SPN perikarya and dendrites. Punctate TTC and GABA immunolabeling were accumulated densely in the neuropil between acid surrounding SPN processes. With electron microscopy, 54% of the axon terminals in the IML (n = 1,337 terminals) were TTC immunolabeled (TTC+), and 25% contained putative neurotransmitter levels of GABA immunolabeling (GABA(+)). On average, GABA(+) terminals had a 76% chance of also being TTC+ and a 62% greater chance of being TTC+ than GABA(-) terminals (P < 0.000001). Axon terminals were just as likely to be TTC+ and/or GABA(+) regardless of whether the dendrites they synapsed on were large (>1 μ M) or small in cross-sectional area or were labeled retrogradely. Sympathetic hyperactivity in tetanus may involve 1) retrograde and transsynaptic transport of TeTx by SPNs and 2) at least in part, an infection of GABAergic terminals in the IML. J. Comp. Neurol. 419: 471-484, 2000. (C) 2000 Wiley-Liss, Inc.

L11 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 2
ACCESSION NUMBER: 2000:120367 CAPLUS
DOCUMENT NUMBER: 133:103239
TITLE: Enkephalin and aFGF Are Differentially Regulated in Rat Spinal Motoneurons after Chemodenervation with Botulinum Toxin
AUTHOR(S): Humm, A. M.; Pabst, C.; Lauterburg, Th.; Burgunder, J.-M.
CORPORATE SOURCE: Laboratory of Neuromorphology, Department of Neurology, Department of Clinical Research, University of Berne, Bern, CH3010, Switz.
SOURCE: Exp. Neurol. (2000), 161(1), 361-372
CODEN: EXNEAC; ISSN: 0014-4886
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Botulinum toxin** is used to induce transient graded paresis by chemodenervation in the treatment of focal hyperkinetic movement disorders. While the mol. events occurring in motoneurons after mech. nerve lesioning leading to muscle paresis are well known, they have been investigated to a lesser extent after chemodenervation. We therefore examd. the expression of enkephalin (ENK), acidic fibroblast growth factor (aFGF), neurotensin (NT), galanin (GAL), **substance P** (SP), vasoactive intestinal polypeptide (VIP), and neuropeptide Y (NPY) in rat spinal motoneurons after chemodenervation of the gastrocnemius. In order to precisely localize the motoneurons targeting the injection site, retrograde tracing was performed in addnl. rats by using Fluorogold injections. ENK expression was upregulated in the region corresponding to the Fluorogold pos. motoneurons, but also on the contralateral side and in

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more distant parts of the spinal cord. The highest upregulation occurred 7 to 14 days after injections and decreased over a period of three months.

At 8 days, aFGF was slightly downregulated in all regions studied, single motoneurons showed NT expression, while expression of GAL, SP, VIP, and NPY could be detected neither in controls nor in toxin-treated animals. These alterations in gene expression were strikingly different from those described after axotomy. Our present findings give addnl. demonstration of the considerable plasticity of the adult spinal cord after

botulinum toxin treatment. (c) 2000 Academic Press.

REFERENCE COUNT: 48

REFERENCE(S): (2) Behari, M; J Neurol Sci 1996, V135, P74 CAPLUS
(3) Bigalke, H; Brain Res 1985, V360, P318 CAPLUS
(4) Bonner, P; Dev Brain Res 1994, V79, P39 CAPLUS
(6) Ceccatelli, S; Neuroscience 1991, V43, P483

CAPLUS

(7) Cortes, R; J Chem Neuroanat 1990, V3, P467 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 15 MEDLINE

DUPLICATE 3

ACCESSION NUMBER: 2000127571 MEDLINE

DOCUMENT NUMBER: 20127571

TITLE: Sensitivity of embryonic rat dorsal root ganglia neurons to

Clostridium botulinum neurotoxins.

AUTHOR: Welch M J; Purkiss J R; Foster K A

CORPORATE SOURCE: Centre for Applied Microbiology and Research, Salisbury, Wiltshire, UK.

SOURCE: TOXICON, (2000 Feb) 38 (2) 245-58.
Journal code: VWT. ISSN: 0041-0101.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200004

ENTRY WEEK: 20000403

AB Clostridium **botulinum** neurotoxins (BoNT) are zinc dependent endopeptidases which, once internalised into the neuronal cytosol, block neurotransmission by proteolysis of membrane-associated proteins putatively involved in synaptic vesicle docking and fusion with the plasma membrane. Although many studies have used a variety of

cellular

systems to study the neurotoxins, most require relatively large amounts of

toxin or permeabilisation to internalise the neurotoxin. We present here a

primary culture of embryonic rat dorsal root ganglia (DRG) neurons that exhibits calcium-dependent **substance P** secretion when depolarised with elevated extracellular potassium and is naturally BoNT sensitive. The DRG neurons showed a different IC50 for each of the toxins tested with a 1000 fold difference between the most and least potent neurotoxins (0.05, 0.3, 30 and approximately 60 nM for A, C, F and B, respectively). BoNT/A cleavage of SNAP-25 was seen as early as 2 h, but **substance P** secretion was not significantly inhibited until 4 h intoxication and the effects of BoNT/A were observed for as

long

as 15 days. This primary neuronal culture system represents a new ^{and} Page 13

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sensitive cellular model for the in vitro study of the **botulinum neurotoxins**.

L11 ANSWER 7 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:256755 BIOSIS
DOCUMENT NUMBER: PREV200000256755
TITLE: Enhanced **Substance P** response of
botulinum toxin-injected opossum lower
esophageal sphincter.
AUTHOR(S): Gaumnitz, Eric A. (1); Bass, Paul; Osinski, Mark A.
CORPORATE SOURCE: (1) Univ of Wisconsin Med Sch, Madison, WI USA
SOURCE: Gastroenterology, (April, 2000) Vol. 118, No. 4 Suppl. 2
Part 1, pp. A154. print..
Meeting Info.: 101st Annual Meeting of the American
Gastroenterological Association and the Digestive Disease
Week. San Diego, California, USA May 21-24, 2000 American
Gastroenterological Association
. ISSN: 0016-5085.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L11 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 4
ACCESSION NUMBER: 2000:172771 CAPLUS
DOCUMENT NUMBER: 133:70034
TITLE: Presynaptic Effects of Botulinum Toxin Type A on the
Neuronally Evoked Response of Albino and Pigmented
Rabbit Iris Sphincter and Dilator Muscles
AUTHOR(S): Ishikawa, H.; Mitsui, Y.; Yoshitomi, T.; Mashimo, K.;
Aoki, S.; Mukuno, K.; Shimizu, K.
CORPORATE SOURCE: School of Medicine, Department of Ophthalmology,
Kitasato University, Sagamihara, Japan
SOURCE: Jpn. J. Ophthalmol. (2000), 44(2), 106-109
CODEN: JJOPA7; ISSN: 0021-5155
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of this study was to investigate the effects of
botulinum toxin type A (botulinum A toxin) on the
autonomic and other nonadrenergic, noncholinergic nerve terminals. The
effects of botulinum A toxin on twitch contractions evoked by elec. field
stimulation (EFS) were studied in isolated albino and pigmented rabbit
iris sphincter and dilator muscles using the isometric tension recording
method. Botulinum A toxin inhibited the fast cholinergic and slow
substance P-ergic component of the contraction evoked by
EFS in the rabbit iris sphincter muscle without affecting the response to
carbachol and **substance P** and these inhibitory effects
were more marked in the albino rabbit than in the pigmented rabbit.
Botulinum A toxin (150 nmol/L) did not affect the twitch contraction
evoked by EFS in the rabbit iris dilator muscle. These data indicated
that botulinum A toxin may inhibit not only the acetylcholine release in
the cholinergic nerve terminals, but also **substance P**
release from the trigeminal nerve terminals of the rabbit iris sphincter
muscle. However, the neurotoxin has little effect on the adrenergic
nerve

terminals of the rabbit iris dilator muscle. Furthermore, the botulinum
A

substanceP-pain

toxin binding to the pigment melanin appears to influence the response quant. in the two types of irides.

REFERENCE COUNT: 18
REFERENCE(S): (1) Bill, A; Acta Physiol Scand 1979, V106, P371
CAPLUS
(3) Ishikawa, H; Arch Pharmacol 1996, V354, P765
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(5) Kelly, R; Ann Rev Neurosci 1979, V2, P399 CAPLUS
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Ophthalmol 1970, V180, P231 CAPLUS
(10) Montecucco, C; Quart Rev Biophys 1995, V28, P423
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:765958 CAPLUS

DOCUMENT NUMBER: 132:74752

TITLE: Sensitivity of embryonic rat dorsal root ganglia
neurons to Clostridium botulinum neurotoxins

AUTHOR(S): Welch, Mary J.; Purkiss, John R.; Foster, Keith A.

CORPORATE SOURCE: Centre for Applied Microbiology and Research,
Salisbury, SP4 0JG, UK

SOURCE: Toxicon (1999), Volume Date 2000, 38(2), 245-258
CODEN: TOXIA6; ISSN: 0041-0101

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Clostridium **botulinum** neurotoxins (BoNT) are zinc
dependent endopeptidases which, once internalized into the neuronal
cytosol, block neurotransmission by proteolysis of membrane-assocd.
proteins putatively involved in synaptic vesicle docking and fusion with
the plasma membrane. Although many studies have used a variety of
cellular systems to study the neurotoxins, most require relatively large
amts. of toxin or permeabilization to interna-Lise the neurotoxin. We
present here a primary culture of embryonic rat dorsal root ganglia (DRG)
neurons that exhibits calcium-dependent **substance P**
secretion when depolarized with elevated extracellular potassium and is
naturally BoNT sensitive. The DRG neurons showed a different IC50 for
each of the toxins tested with a 1000 fold difference between the most

and

least potent neurotoxins (0.05, 0.3, 30 and .apprx.60 nM for A, C, F and
B, resp.). BoNT/A cleavage of SNAP-25 was seen as early as 2 h, but
substance P secretion was not significantly inhibited
until 4 h intoxication and the effects of BoNT/A were obsd. for as long

as

15 days. This primary neuronal culture system represents a new and
sensitive cellular model for the in vitro study of the **botulinum**
neurotoxins.

REFERENCE COUNT: 34

REFERENCE(S): (1) Ahnert Hilger, G; Neuroscience 1993, V53, P547
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(2) Bi, G; J Cell Biol 1995, V131, P1747 CAPLUS
(3) Blasi, J; Nature 1993, V365, P160 CAPLUS
(4) Boyd, R; J Biol Chem 1995, V270, P18216 CAPLUS
(5) de Paiva, A; J Biol Chem 1993, V268, P20838

CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 5
 ACCESSION NUMBER: 2000:132672 CAPLUS
 DOCUMENT NUMBER: 133:54732
 TITLE: Buforin I, a natural peptide, inhibits botulinum
 neurotoxin B activity in vitro
 AUTHOR(S): Garcia, Gregory E.; Moorad, Deborah R.; Gordon,
 Richard K.
 CORPORATE SOURCE: Division of Biochemistry, Walter Reed Army Institute
 of Research, Washington, DC, 20307, USA
 SOURCE: J. Appl. Toxicol. (1999), 19(Suppl. 1), S19-S22
 CODEN: JJATDK; ISSN: 0260-437X
 PUBLISHER: John Wiley & Sons Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB **Botulinum neurotoxin B (BoNT/B)** serotype specifically
 cleaves between the amino acids glutamine and phenylalanine (Q and F
 bond)
 in position 76-77 of synaptobrevin (VAMP2). We evaluated peptides that
 contain the QF cleavage site but are not identical in primary structure
 to
 the VAMP2 sequence surrounding the QF site for both inhibition of BoNT/B
 proteolytic activity and as substrates for BoNT/B. A reverse-phase
 high-performance liq. chromatog. (RP-HPLC) method was used to measure
 digested peptides. A dose as high as 600 .mu.M of **substance**
P, and 11-amino acid peptide contg. the QF bond, was neither a
 substrate nor inhibitor of BoNT/B in our assay, suggesting that more than
 the QF bond is required to be recognized by BoNT/B. Buforin I (B-I, QF
 site 24-25) is 39 amino acids in length, and sequence comparison of B-I
 and VAMP2 indicated a similarity of 18% for conserved amino acids around
 the QF site. Furthermore, computer-aided secondary structure
 computations
 predict .alpha.-helical structures flanking the QF site for VAMP2 and for
 the upstream sequence of B-I. Although predictions for the downstream
 sequence give nearly equal tendencies for .alpha.-helical and
 .beta.-sheet
 structures, G. Yi et al. (1996) showed that the downstream sequence is
 likely to be the .alpha.-helix based on their examn. of buforin II (B-II,
 a 21-amino acid subset of B-I (16-36)), which includes the QF site and
 the
 downstream sequence of B-I. Buforin I was found not to be a substrate
 for
 BoNT/B; however, B-I dose dependently and competitively inhibited BoNT/B
 activity, yielding IC50 = 1.times.10-6 M. In contrast, B-II was not a
 substrate for BoNT/B and exhibited only 25% of the B-I inhibition of
 BoNT/B. Two addnl. B-I deletion peptides were tested for inhibition of
 BoNT/B proteolysis: peptide 36 (36 mer; contg. B-I amino acids 1-36) and
 peptide 24 (24 mer; B-I amino acids 16-39). Peptide 24 had a similar
 inhibitory effect to B-II (.apprx.25% of B-I) but peptide 36 was almost
 50% as potent as B-I. These findings suggest that the buforin tertiary
 structure is important for the inhibitory activity of these peptides for
 BoNT/B.
 REFERENCE COUNT: 15
 REFERENCE(S): (1) Adler, M; Toxicon 1997, V35, P1089 CAPLUS
 (2) Deshpande, S; Toxicon 1995, V33, P551 CAPLUS
 (3) Garnier, J; Methods Enzymol 1996, V266, P540
 CAPLUS

substanceP-pain

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(7) Montecucco, C; Mol Microbiol 1994, V13, P1 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 6
ACCESSION NUMBER: 1997:615391 CAPLUS
DOCUMENT NUMBER: 127:288483
TITLE: Capsaicin stimulates release of substance P from
dorsal root ganglion neurons via two distinct
mechanisms
AUTHOR(S): Purkiss, John R.; Welch, Mary J.; Doward, Sarah;
Foster, Keith A.
CORPORATE SOURCE: CAMR (Centre of Applied Microbiology and Research),
Salisbury, Wiltshire, SP4 0JG, UK
SOURCE: Biochem. Soc. Trans. (1997), 25(3), 542S
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this report, the authors describe both extracellular Ca²⁺-dependent
and

-independent mechanisms of capsaicin-induced release of **substance P** from cultured embryonic rat dorsal root ganglion neurons. Further, the authors describe the differing **botulinum toxin A** sensitivity of these two mechanisms. Rat dorsal root ganglion neurons (DRGs) were prepd. from 14-16 days gestation embryos. Release of **substance P** was measured and then total **substance P** was measured following capsaicin or KCl stimulation in the absence of Ca²⁺ and in the presence of Ca²⁺. **Substance P** immunoreactivity was measured using an enzyme immunoassay kit. **Botulinum neurotoxin (BoNT/A)** cleavage of SNAP-25 was measured in cells following 18-20 h exposure to toxin. From the results the authors found that capsaicin is able to

evoke

release of **substance P** from DRGs by two mechanisms. The first mechanism is Ca²⁺-dependent, maximally stimulated by 0.3. μ M capsaicin and requires intact SNAP-25 for optimum release. The second mechanism is Ca²⁺-independent, becomes activated at 3-10. μ M capsaicin and is insensitive to BoNT/A so it induces release through a mechanism that does not have SNAP-25 as an essential component.

L11 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 7
ACCESSION NUMBER: 1996:121571 CAPLUS
DOCUMENT NUMBER: 124:172549
TITLE: Effect of muscle denervation on the expression of
substance P in the ventral raphe-spinal pathway of
the
rat
AUTHOR(S): Bergh, P. Van den; Beukelaer, M. De; Deconinck, N.
CORPORATE SOURCE: Laboratoire de Biologie Neuromusculaire, Service de
Neurologie, Cliniques Universitaires St-Luc,
Universite de Louvain, 10 Avenue Hippocrate,
Brussels,
B-1200, Belg.
SOURCE: Brain Res. (1996), 707(2), 206-12
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal

substanceP-pain

LANGUAGE: English

AB The medullary raphe nuclei, wherein serotonin coexists with **substance P** (SP) and TSH-releasing hormone, innervate lower motor neurons in the spinal cord ventral horn by the ventral raphe-spinal pathway. Destruction of the ventral raphe-spinal pathway is assocd. with deficient recovery of denervated muscle, indicating that it may exert a trophic effect upon lower motor neurons. To det. whether SP could be a trophic factor for lower motor neurons within the ventral raphe-spinal pathway, the effect of muscle denervation with **botulinum toxin** type A on SP-encoding .beta.-preprotachykinin mRNA in the rat medullary raphe was examd. by in situ hybridization histochem. Silver grain d. over hybridized medullary raphe neurons was increased by up to 11%, although the no. of hybridized neurons did not change in denervated as compared to control rats. Increased SP gene expression in the medullary raphe in response to motor unit lesioning suggests that raphe-spinal SP may be trophic to lower motor neurons.

L11 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 8

ACCESSION NUMBER: 1994:263475 CAPLUS

DOCUMENT NUMBER: 120:263475

TITLE: Exogenous zinc ion is required for inhibitory activity

of **botulinum neurotoxin** C1 against norepinephrine release and its endopeptidase activity toward **substance P**

AUTHOR(S): Yokosawa, Noriko; Suga, Kei; Kimura, Koichi; Tsuzuki, Kayo; Fujii, Nobuhiro; Oguma, Keiji; Yokosawa, Hideyoshi

CORPORATE SOURCE: Sch. Med., Sapporo Med. Univ., Sapporo, 060, Japan

SOURCE: Biochem. Mol. Biol. Int. (1994), 32(3), 455-63

CODEN: BMBIES

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Botulinum neurotoxin** C1 inhibited Ca²⁺-evoked norepinephrine secretion from digitonin-permeabilized PC12 cells. The inhibition by the neurotoxin was dependent on the presence of Zn²⁺ added exogenously. This zinc-dependent inhibition was neutralized by monoclonal

antibodies that recognize the sites close to the putative zinc-binding motif in the light chain. The neurotoxin was found to have an endopeptidase activity toward small peptide, **substance P**

. The presence of exogenous Zn²⁺ was also indispensable to the full expression of this endopeptidase activity. Thus, both the inhibition of neurotransmitter release by the C1 neurotoxin and its endopeptidase activity are dependent on exogenous Zn²⁺, which suggests a strong link between the two activities.

L11 ANSWER 14 OF 15 MEDLINE

DUPLICATE 9

ACCESSION NUMBER: 82048151 MEDLINE

DOCUMENT NUMBER: 82048151

TITLE: BaCl₂-induced contractions in the guinea pig ileum longitudinal muscle: role of presynaptic release of neurotransmitters and Ca²⁺ translocation in the postsynaptic membrane.

AUTHOR: Clement J G

substanceP-pain

SOURCE: CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, (1981 Jun)

59 (6) 541-7.

Journal code: CJM. ISSN: 0008-4212.

PUB. COUNTRY: Canada

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 198203

AB Early studies indicated that the BaCl₂-induced contractions in the guinea pig ileum longitudinal muscle strip (GPI-LMS) were, in part, neuronal in origin. However, recent studies have suggested that BaCl₂-induced contractions were produced by an action directly on the smooth muscle membrane. The purpose of this study was to investigate the mechanism of the BaCl₂ contractions in the GPI-LMS. **Botulinum toxin** (5 x 10⁵ MLD/mL), which blocks the electrically induced release of acetylcholine (ACh), hemicholinium-3 (HC-3; 110 micro M), which blocks

ACh synthesis, tetrodotoxin (TTX; 60 nM), which blocks Na⁺ channels, black widow spider venom, which depletes the presynaptic neuron of neurotransmitter, and atropine (2.9 micro M), a potent muscarinic antagonist, had no effect on the BaCl₂ contractions. Densitization of the GPI-LMS to **substance P** did not affect the BaCl₂ contraction. In Ca²⁺-free buffer the BaCl₂ dose-response curve was shifted to the right. In Ca²⁺-free solution the time to 50% inhibition of the contractile response to ACh (73 nM) and BaCl₂ (1.16 mM) was 3.7 and 125 min, respectively. The D 600 IC₅₀ for ACh and BaCl₂ contractions was 220 and 130 nM, respectively. In Ca²⁺-free buffer either EGTA (0.53 mM)

or D 600 (1 micro M) were potent inhibitors of BaCl₂ contractions. These results suggest that in the GPI-LMS the BaCl₂ response is not mediated by a release of ACh (or **substance P**) because inhibitors of ACh release, synthesis, and receptors do not affect the responses. Also, the BaCl₂ contraction is not due to activation of Na⁺ channels because TTX is without effect. The BaCl₂-induced contraction appears to

be mainly due to the movement of membrane bound Ca²⁺ through D 600 sensitive Ca²⁺ channels with extracellular Ca²⁺ and possible passage of Ba²⁺ ions intracellularly playing relatively minor roles.

L11 ANSWER 15 OF 15 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1976:180040 BIOSIS

DOCUMENT NUMBER: BA62:10040

TITLE: CONTRACTION AND RELAXATION OF THE RETRACTOR PENIS MUSCLE AND PENILE ARTERY OF THE BULL A STUDY OF EFFECTS OF DRUGS AND TRANS MURAL NERVE STIMULATION ON ISOLATED SMOOTH

MUSCLE

STRIPS.

AUTHOR(S): KLINGE E; SJOSTRAND N O

SOURCE: ACTA PHYSIOL SCAND SUPPL, (1974 (RECD 1975)) (420), 1-88.

CODEN: APSSAD. ISSN: 0302-2994.

FILE SEGMENT: BA; OLD

LANGUAGE: Unavailable

AB The effects of field stimulation and various endogenous compounds and drugs on autonomic nerves or receptors were investigated on isolated strips of the retractor penis muscle and the penile artery of the

substanceP-pain

Excitatory and inhibitory responses to field stimulation and secondary contraction were abolished by tetrodotoxin or local anesthetic drugs. The excitatory response to field stimulation was inhibited or abolished by .alpha.-adrenoceptor and adrenergic neuron blocking agents and was enhanced by inhibitors of neuronal noradrenaline uptake. Noradrenaline and adrenaline contracted the retractor penis and the penile artery. This effect was abolished by .alpha.-adrenoceptor blocking agents. After .alpha.-receptor blockade adrenaline, noradrenaline and isoprenaline produced relaxation which was prevented by .beta.-adrenoceptor blocking agents. The inhibitory response to field stimulation was not prevented by antimuscarinic, ganglionic blocking or neuromuscular blocking drugs or counteracted by **botulinum toxin** or hemicholinium and was apparently unaffected by physostigmine. It was uncovered by adrenergic neuron blocking agents. Acetylcholine caused contraction of the smooth muscle, suppression of the excitatory response to field stimulation and a brief relaxation sometimes preceded by a rapid contraction and resembling the effect of transmural nerve stimulation. The first 2 effects of acetylcholine were emulated by pilocarpine and prevented by antimuscarinic drugs; the 3rd effect was prevented by hexamethonium and emulated by nicotine. Nicotine-induced relaxations were prevented by ganglionic blocking agents and by local anesthetics. All acetylcholine effects, particularly the last, required high concentrations. Histamine and 5-hydroxytryptamine contracted both penis and artery. The inhibitory response to field stimulation were not blocked by antihistamines or serotonin antagonists. ATP contracted the penis but relaxed the penile artery. Desensitization to ATP abolished or reversed this relaxation, but had no effect on the inhibitory response to field stimulation. No overt effects on the retractor penis and penile artery were obtained with .gamma. aminobutyric acid [GABA], glycine, glutamic acid, aspartic acid or several other amino acids. Prostaglandins (PG) E1 and E2 relaxed the retractor penis; PGF2.alpha. contracted it. All were powerful stimulants of arterial smooth muscle. Prolonged exposure to inhibitors of PG synthesis did not suppress inhibitory responses to field stimulation. Minute concentrations of bradykinin contracted the retractor penis but had almost no effect on the penile artery. **Substance P** contracted the muscles. Posterior pituitary hormones had no overt effect on the retractor penis but contracted the penile artery.

=> d his

(FILE 'HOME' ENTERED AT 18:11:07 ON 08 DEC 2000)

FILE 'CAPLUS, MEDLINE, EMBASE, BIOSIS, SCISEARCH' ENTERED AT 18:11:36 ON 08 DEC 2000

L1 15337 S BOTULINUM (W) (TOXIN OR NEUROTOXIN)
L2 738 S CLOSTRIDIAL NEUROTOXIN
L3 276657 S NEUROPEPTIDE OR NEUROTRANSMITTER OR NEUROTRANSMISSION
COMPOUN
L4 94483 S TACHYKININ OR SUBSTANCE (W) P
L5 5148 S PHYSALAEMIN OR KASSININ OR UPEROLEIN OR ELEDOSIN OR
SUBSTANC

substanceP-pain

L6 688 S L1 (P) L3
L7 231 DUPLICATE REMOVE L6 (457 DUPLICATES REMOVED)
L8 4 S L7 (P) (CONJUGATE OR COVALENT)
L9 4 S L7 (P) (LINK OR LINKAGE)
L10 44 S L1 (P) L4
L11 15 DUPLICATE REMOVE L10 (29 DUPLICATES REMOVED)

=> s 11 (p) 15

L12 0 L1 (P) L5

=> s 12 (p) 13

L13 223 L2 (P) L3

=> duplicate remove

ENTER L# LIST OR (END):113

DUPLICATE PREFERENCE IS 'CAPLUS, MEDLINE, EMBASE, BIOSIS, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n

PROCESSING COMPLETED FOR L13

L14 104 DUPLICATE REMOVE L13 (119 DUPLICATES REMOVED)

=> s 114 (p) (conjugate or covalent or link or linkage)

L15 3 L14 (P) (CONJUGATE OR COVALENT OR LINK OR LINKAGE)

=> d 115 1-3 ibib abs

L15 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 2000:282545 CAPLUS

DOCUMENT NUMBER: 133:54741

TITLE: Inhibition of vesicular secretion in both neuronal
and

AUTHOR(S): nonneuronal cells by a retargeted endopeptidase
derivative of Clostridium botulinum neurotoxin type A
Chaddock, John A.; Purkiss, John R.; Friis, Lorna M.;
Broadbridge, Janice D.; Duggan, Michael J.; Fooks,
Sarah J.; Shone, Clifford C.; Quinn, Conrad P.;
Foster, Keith A.

CORPORATE SOURCE: Centre for Applied Microbiology and Research,
Salisbury, SP4 0JG, UK

SOURCE: Infect. Immun. (2000), 68(5), 2587-2593
CODEN: INFIBR; ISSN: 0019-9567

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Clostridial neurotoxins** potently and specifically
inhibit **neurotransmitter** release in defined cell types by a
mechanism that involves cleavage of specific components of the vesicle
docking/fusion complex, the SNARE complex. A deriv. of the type A
neurotoxin from C. botulinum (termed LHN/A) that retains catalytic
activity can be prepd. by proteolysis. The LHN/A, however, lacks the
putative native binding domain (HC) of the neurotoxin and is thus

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to bind to neurons and effect inhibition of **neurotransmitter** release. Here, the authors report the chem. conjugation of LHN/A to an alternative cell-binding ligand, wheat germ agglutinin (WGA). When applied to a variety of cell lines, including those that are ordinarily resistant to the effects of neurotoxin, WGA-LHN/A **conjugate** potently inhibits secretory responses in those cells. Inhibition of release is demonstrated to be ligand-mediated and dose-dependent and to occur via a mechanism involving endopeptidase-dependent cleavage of the natural botulinum neurotoxin type A substrate. These data confirm that the function of the HC domain of C. botulinum neurotoxin type A is limited to binding to cell surface moieties. The data also demonstrate that the endopeptidase and translocation functions of the neurotoxin are effective in a range of cell types, including those of nonneuronal origin. These observations lead to the conclusion that a clostridial endopeptidase **conjugate** that can be used to investigate SNARE-mediated processes in a variety of cells has been successfully generated.

REFERENCE COUNT: 30

REFERENCE(S): (1) Black, J; Neuroscience 1987, V23, P767 CAPLUS
(2) Blasi, J; Nature 1993, V365, P160 CAPLUS
(3) Boyd, R; J Biol Chem 1995, V270, P18216 CAPLUS
(4) Fitzgerald, D; Targeted Diagn Ther 1992, V7, P447 CAPLUS
(6) Gabor, JF; J Controlled Release 1998, V55, P131 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:249106 CAPLUS

DOCUMENT NUMBER: 130:276767

TITLE: Conjugates of galactose-binding lectins and clostridial neurotoxins as analgesics

INVENTOR(S): Duggan, Michael John; Chaddock, John Andrew

PATENT ASSIGNEE(S): The Speywood Laboratory Limited, UK; Microbiological Research Authority

SOURCE: PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9917806	A1	19990415	WO 1998-GB3001	19981007
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ,			
	RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG		
AU 9893574	A1	19990427	AU 1998-93574	19981007
ZA 9809138	A	19990527	ZA 1998-9138	19981007
EP 996468	A1	20000503	EP 1998-946571	19981007

substanceP-pain

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI

PRIORITY APPLN. INFO.:

GB 1997-21189 19971008
WO 1998-GB3001 19981007

AB A class of novel agents that are able to modify nociceptive afferent function is provided. The agents may inhibit the release of neurotransmitters from discrete populations of neurons and thereby reduce or preferably prevent the transmission of afferent pain signals from peripheral to central pain fibers. They comprise a galactose-binding lectin linked to a deriv. of a clostridial neurotoxin. The deriv. of the clostridial neurotoxin comprises the L-chain, or a fragment thereof, which includes the active proteolytic enzyme domain of the light (L) chain, linked to a mol. or domain with membrane-translocating activity. The agents may be used in or as pharmaceuticals for the treatment of pain, particularly chronic pain.

REFERENCE COUNT: 6

REFERENCE(S):

- (1) Allergan Inc; WO 9428923 A 1994
- (2) Dolly, J; WO 9532738 A 1995
- (3) Foster, K; WO 9633273 A 1996
- (4) Foster, K; WO 9807864 A 1998
- (6) Streit; J Histochem Cytochem 1985, V33(10), P1042
CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 3 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000346869 EMBASE

TITLE: A conjugate composed of nerve growth factor coupled to a non-toxic derivative of Clostridium botulinum neurotoxin type A can inhibit neurotransmitter release in vitro.

AUTHOR: Chaddock J.A.; Purkiss J.R.; Duggan M.J.; Quinn C.P.;
Shone

C.C.; Foster K.A.

CORPORATE SOURCE: J.R. Purkiss, Centre for Applied Microbiology/Res., Porton Down, Salisbury, Wiltshire SP4 0JG, United Kingdom

SOURCE: Growth Factors, (2000) 18/2 (147-155).

Refs: 24

ISSN: 0897-7194 CODEN: GRFAEC

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 030 Pharmacology

037 Drug Literature Index

039 Pharmacy

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Nerve growth factor (NGF) receptor binding, internalisation and transportation of NGF has been identified as a potential route of delivery

for other molecules. A derivative of Clostridium botulinum neurotoxin type

A (LH(N)) that retains catalytic activity but has significantly reduced cell-binding capability has been prepared and chemically coupled to NGF. Intact **clostridial neurotoxins** potentially inhibit neurotransmitter release at the neuromuscular junction by proteolysis of specific components of the vesicle docking/fusion complex. Here we report that the NGF-LH(N)/A **conjugate**, when applied to PC12 cells, significantly inhibited **neurotransmitter** release and

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cleaved the type A toxin substrate. This work represents the successful use of NGF as a targeting moiety for the delivery of a neurotoxin fragment.

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(FILE 'HOME' ENTERED AT 18:11:07 ON 08 DEC 2000)

FILE 'CAPLUS, MEDLINE, EMBASE, BIOSIS, SCISEARCH' ENTERED AT 18:11:36 ON 08 DEC 2000

L1 15337 S BOTULINUM (W) (TOXIN OR NEUROTOXIN)
L2 738 S CLOSTRIDIAL NEUROTOXIN
L3 276657 S NEUROPEPTIDE OR NEUROTRANSMITTER OR NEUROTRANSMISSION
COMPOUN
L4 94483 S TACHYKININ OR SUBSTANCE (W) P
L5 5148 S PHYSALAEMIN OR KASSININ OR UPEROLEIN OR ELEDOISIN OR
SUBSTANC
L6 688 S L1 (P) L3
L7 231 DUPLICATE REMOVE L6 (457 DUPLICATES REMOVED)
L8 4 S L7 (P) (CONJUGATE OR COVALENT)
L9 4 S L7 (P) (LINK OR LINKAGE)
L10 44 S L1 (P) L4
L11 15 DUPLICATE REMOVE L10 (29 DUPLICATES REMOVED)
L12 0 S L1 (P) L5
L13 223 S L2 (P) L3
L14 104 DUPLICATE REMOVE L13 (119 DUPLICATES REMOVED)
L15 3 S L14 (P) (CONJUGATE OR COVALENT OR LINK OR LINKAGE)

=> s 12 (p) 14

L16 2 L2 (P) L4

=> d 116 1-2 ibib abs

L16 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:249106 CAPLUS

DOCUMENT NUMBER: 130:276767

TITLE: Conjugates of galactose-binding lectins and clostridial neurotoxins as analgesics

INVENTOR(S): Duggan, Michael John; Chaddock, John Andrew

PATENT ASSIGNEE(S): The Speywood Laboratory Limited, UK; Microbiological Research Authority

SOURCE: PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

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WO 9917806	A1	19990415	WO 1998-GB3001	19981007

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP

substanceP-pain

KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW,
MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ,

TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9893574 A1 19990427 AU 1998-93574 19981007
ZA 9809138 A 19990527 ZA 1998-9138 19981007
EP 996468 A1 20000503 EP 1998-946571 19981007

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI

PRIORITY APPLN. INFO.:

GB 1997-21189 19971008
WO 1998-GB3001 19981007

AB A class of novel agents that are able to modify nociceptive afferent
function is provided. The agents may inhibit the release of
neurotransmitters from discrete populations of neurons and thereby reduce
or preferably prevent the transmission of afferent pain signals from
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which

includes the active proteolytic enzyme domain of the light (L) chain,
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6

REFERENCE(S):

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- (3) Foster, K; WO 9633273 A 1996
- (4) Foster, K; WO 9807864 A 1998
- (6) Streit; J Histochem Cytochem 1985, V33(10), P1042
CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 2 OF 2 SCISEARCH COPYRIGHT 2000 ISI (R)

ACCESSION NUMBER: 1999:910001 SCISEARCH

THE GENUINE ARTICLE: 257VL

TITLE: Sensitivity of embryonic rat dorsal root ganglia neurons
to Clostridium botulinum neurotoxins

AUTHOR: Welch M J; Purkiss J R (Reprint); Foster K A

CORPORATE SOURCE: PUBL HLTH LAB SERV, CTR APPL MICROBIOL & RES, SALISBURY
SP4 0JG, WILTS, ENGLAND (Reprint); PUBL HLTH LAB SERV,

CTR

APPL MICROBIOL & RES, SALISBURY SP4 0JG, WILTS, ENGLAND

COUNTRY OF AUTHOR: ENGLAND

SOURCE: TOXICON, (FEB 2000) Vol. 38, No. 2, pp. 245-258.
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD,
LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.
ISSN: 0041-0101.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 34

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Clostridium botulinum neurotoxins (BoNT) are zinc dependent
endopeptidases which. once internalised into the neuronal cytosol, ^{block} _{Page 25}

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neurotransmission :by proteolysis of membrane-associated proteins
putatively involved in synaptic vesicle docking and fusion with the
plasma membrane. Although many studies have used a variety of cellular systems
to study the neurotoxins, most require relatively large amounts of toxin dr
permeabilisation to internalise the neurotoxin. We present here a primary
culture of embryonic rat dorsal root ganglia (DRG) neurons that exhibits
calcium-dependent substance P secretion when depolarised with elevated
extracellular potassium and is naturally BoNT sensitive. The DRG neurons
showed a different IC50 for each of the toxins tested with a 1000 fold
difference between the most and least potent neurotoxins (0.05, 0.3,30
and similar to 60 nM for A, C, F and B, respectively). BoNT/A cleavage of
SNAP-25 was seen as early as 2 h, but substance P secretion was not
significantly inhibited until 4 h intoxication and the effects of BoNT/A
were observed for as long as 15 days. This primary neuronal culture
system represents a new and sensitive cellular model for the ill vitro study of
the botulinum neurotoxins. (C) 1999 Elsevier Science Ltd. All rights
reserved.

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L17 0 L2 (P) L5

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